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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,231	08/19/2004	Paul Richard Gellert	ASZD-P01-724	3886

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 08/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/505,231	GELLERT ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-19 are currently pending and are the subject of this Office Action.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

No support is seen the foreign priority documents 0204392.5 and 0212462.6 for the instantly claimed compositions comprising Iressa and a water-soluble cellulose ether or an ester of a water-soluble cellulose ether. As such, the earliest effective filing date has been determined to be June 11, 2002 (filing date of foreign priority document 0213267.8).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4-6, 8-11, 13, 16-17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 4,344,934 (Issued August 17, 1982) (hereinafter "'934") in view of WO 98/38984 (Published September 11, 1998)(hereinafter "WO").

The instant claims are drawn to pharmaceutical compositions comprising the drug 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (hereinafter, Iressa) and water-soluble cellulose ethers or esters of water-soluble cellulose ethers.

The '934 patent discloses novel compositions comprising wetted mixtures of poorly soluble drugs with water-soluble polymers (Abstract). The problem to be solved is stated in Column 1, Lines 23-26 wherein the authors state that many drugs give incomplete and irregular absorption when taken orally, particularly poorly water-soluble or water insoluble compounds. To solve this problem, compositions comprising a mixture of drug with a "pharmacologically acceptable water soluble polymer" and a minor amount of a "wetting agent selected from anionic and cationic surfactants" are disclosed (col. 3, lines 17-22).

Particularly suitable polymers such as hydroxypropylmethyl cellulose and hydroxypropyl cellulose are disclosed in Column 3, Lines 25-30. The preferred

surfactants (*i.e.* wetting agents) are selected from anionic (*e.g.* sodium lauryl sulfate, sodium laurate) and cationic surfactants (col. 3, lines 30-34). In another embodiment, the invention disclosed in '934 includes a method of treating mammals with the compositions of the invention in order to increase the bioavailability of the drug (col. 3, lines 35-38). The compositions of the invention can also include fillers, binders, disintegrants and other pharmaceutically acceptable excipients (Example 17 in col. 15).

The '934 patent does not disclose that the compositions disclosed therein can comprise drugs such as the quinazoline, Iressa, as claimed in the instant invention.

However, WO discloses formulations including liquid, semi-solid or solid pharmaceutical formulations that improve the oral bioavailability of hydrophobic pharmaceutical agents, such as quinazoline-, nitrothiazole- and indolinone-based compounds (Abstract). Preferred quinazoline compounds are disclosed as represented by formula I (page 10) and formula II (page 15). The reference discloses that, "Certain potential pharmaceuticals are hydrophobic and typically have very low aqueous solubility and hence low oral bioavailability" (page 2, lines 9-11).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a pharmaceutical composition comprising the instantly quinazoline and a water-soluble cellulose ether or ester of a water-soluble cellulose ether. Quinazolines were known in the art to have low aqueous solubility and hence low bioavailability as disclosed in WO. A solution to the problem of poorly soluble drugs is to formulate wetted mixtures of poorly soluble drugs with water-soluble polymers as disclosed in '934.

The skilled artisan would have been imbued with at least a reasonable expectation that a composition of Iressa in a water-soluble polymer such as hydroxypropylmethyl cellulose or hydroxypropyl cellulose (as disclosed in '934) would lead to increased bioavailability of the drug due to its improved solubility. The motivation to combine the references is found in the disclosure of WO wherein quinazolines are taught to be hydrophobic and typically have very low aqueous solubility and hence low oral bioavailability. Thus, a person of ordinary skill in the art would have been motivated to add wetting agents and polymers such as hydroxypropylmethyl cellulose and hydroxypropyl cellulose as disclosed in '934 to a composition of Iressa in order to increase solubility and improve the bioavailability of the quinazoline drug.

Claims 1-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 4,344,934 and WO 98/38984 as applied to claims 1-2, 4-6, 8-11, 13, 16-17 and 19 above, and further in view of U.S. Patent No. 6,287,599 (Issued September 11, 2001)(hereinafter '599).

'934 and WO disclose as above. '599 discloses pharmaceutical compositions that have minimized pH-dependent dissolution profiles (Abstract). These compositions contain sustained release agents (*e.g.* hydroxypropyl methylcellulose), enteric agents (*e.g.* hydroxypropyl methylcellulose phthalate), bulking agents (*e.g.* mannitol and lactose), disintegrating agents (*e.g.* microcrystalline cellulose, crospovidone and sodium starch glycolate), antiadherants and glidants (*e.g.* sodium lauryl sulfate), lubricants (*e.g.* magnesium stearate), and binding agents (*e.g.* polyvinyl pyrrollidone and hydroxypropyl

methylcellulose) (cols. 1-3). These excipients are provided in amounts that are within the ranges disclosed in the instant claims (*e.g.* in instant claim 12). The table below is provided to demonstrate the overlap between the '599 patent and the instant claims.

U.S. Patent No. 6,287,599	**Instant Claim 12**
Active Agent (col. 1, lines 40-51) *1 to 40 wt. %*	(a) The Agent *10 to 80 parts*
Antiadherant or glidant (col. 2, lines 59-64) *0.5 to 5 wt. %*	(b) Anionic Surfactant *0.05 to 5 parts*
Bulking Agents (col. 2, lines 39-49) *10 to 50 wt. %*	(c) Fillers *10 to 60 parts*
Disintegrating Agents (col. 2, lines 50-58) *1 to 15 wt. %*	(d) Disintegrants *1 to 10 parts*
Binding Agents (col. 3, lines 8-13) *0.5 to 5 wt. %*	(e) Binder *1 to 20 parts*
Lubricants (col. 2, line 65 to col. 3, line 7) *0.5 to 5 wt. %*	(f) Lubricant *0 to 3 parts*

Instant claim 12 recites the limitation wherein "at least one of the components selected from (d) or (e) contains a water-soluble cellulose ether selected from hydroxypropyl methylcellulose and carboxymethylcellulose sodium." However, '599 recites hydroxypropyl methylcellulose as one of the binding agents that may be employed in the compositions disclosed therein (col. 3, lines 8-13). Instant claim 3 requires an ester of hydroxypropyl methylcellulose or hydroxypropyl cellulose that "carries one or more ester groups selected from acetate, succinate, phthalate, isophthalate, terephthalate and trimellitate." However, '599 recites enteric agents including hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate and succinate (col. 2, lines 23-27).

The compositions of the '599 patent are adapted for oral administration in the form of tablets and the tablets may be coated, if desired (col. 3, lines 14-23 and col. 3, line 59 to col. 4, line 4).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the excipients disclosed in '599 to formulate a oral pharmaceutical composition comprising Iressa. The motivation to do so is found in the '599 patent wherein the authors disclose that the compositions disclosed therein are suitable for a "pharmaceutically active agent that is pH dependent" (Abstract, Claims and col. 1, lines 5-57).[1] The quinazoline, Anagrelide HCl, is one of the preferred pH-dependent agents in the '599 patent (see Example 2 and Claim 7). The skilled artisan would have been imbued with at least a reasonable expectation that a composition comprising Iressa and the excipients disclosed in the '599 patent would lead to decreased pH dependence on the solubility of the agent in GI track when administered to a human patient.

When taken together with the disclosures of '934 and WO, the instantly claimed compositions comprise excipients that were known in the art to be useful in the formulation of compositions of pH-dependent and poorly water-soluble agents.

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 4,344,934, WO 98/38984 and U.S. 6,287,599 as applied to claims 1-14 and 16-18

[1] Examiner notes that on page 2, lines 22-25, applicants of the instant invention state that the solubility of Iressa is highly pH dependent due to the two basic groups of the agent (a quinazoline).

above, and further in view of U.S. Patent No. 5,641,536 (Issued June 24, 1997)(hereinafter '536).

'934, WO, and '599 disclose as above. The '536 patent discloses a tablet coating method comprising polymeric coating ingredients (Abstract). The polymer coating ingredients comprise a coating polymer and "may include plasticizers, colorants, opacifiers, glidants, flavoring agents, diluents, fillers, bulking agents and other ingredients suitable for use in polymeric coatings" (col. 4, lines 29-33). Suitable polymers are disclosed to include cellulose ethers, including hydroxypropyl methylcellulose (col. 4, lines 33-35). A plasticizer is disclosed as being useful to promote softening and ease of deformation of the polymer whereas the colorants, opacifiers and glidants improve appearance and other characteristics of the coating (col. 4, lines 53-55 and col. 4 line 66 to col. 5, line 1). Talc is disclosed as being a useful glidant (*i.e.* dispersion aid) for improved processing and to reduce coating tackiness (col. 5, lines 15-20). Thus, the reference discloses a tablet film coating comprising all of the excipients recited in instant claim 15.

Composition 2C in the table provided under Example 2 of the '536 patent discloses a film coating composition comprising 12% cellulose ether, 2% propylene glycol (plasticizer), 5% titanium dioxide (opacifier) and 5% talc (dispersion aid), among other additives. These amounts are based on the weight % of the film coating, not the total weight of a pharmaceutical composition onto which the film coating is applied. Although the amounts of film coating additives are not explicitly disclosed, it is the Examiner's position that the amounts recited in instant claim 15 are inherent in the

disclosure of '536. For example, the amounts of film coating additives in '536 are based on the total weight of the film coating composition whereas the amounts recited in instant claim 15 are based on the total weight of the composition. When applied to a tablet in the form of a film coating, depending on the amount applied and the thickness applied, the total amount of film coating additives will be within the range recited in instant claim 15.[2] This is especially true given that that once dissolved in an aqueous media to form a coating solution, the coating polymer is preferably in a concentration of from 3 to 15% (col. 6, lines 50-55). Thus, if a 3 to 15% solution of polymeric coating is sprayed onto a tablet, the total amount of additives present in said coating will be substantially less than that recited in Composition 2C, for example.

Thus, the instantly claimed solid pharmaceutical compositions, including the composition recited in instant claim 15 that comprises a film coating, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. The instant compositions differ from the prior art in the active agent present in the compositions (*i.e.* Iressa). However, the specific additives (*e.g.* excipients, polymers and coatings) were well known in the art at the time the invention was made. As discussed *supra*, oral formulations of Iressa comprising known pharmaceutical excipients and methods would have been obvious to one of ordinary skill in the art.

[2] It is noted that the film coating recited in instant claim 15 only requires that 0.5 to 3% (based on total weight of the composition) water-soluble cellulose ether be present. The other additives need not be present at all as they can be in amounts from 0 to 0.5%.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson
Examiner
Art Unit 1614

July 18, 2006

Ardin H. Marschel 7/27/06

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER